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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/840,746	04/23/2001	Huei-Mei Chen	PC-0039 US	5003

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/23/2003 12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/840,746	CHEN ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *7-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 1-6, SEQ ID NO:2 and polynucleotides encoding SEQ ID NO:1, naturally occurring variants and complement thereof are being examined.

This application contains claims drawn to an invention nonelected with traverse in Paper No.9. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The following are the remaining rejections.

REJECTION UNDER 35 USC 101, UTILITY

Rejection under 35 USC 101, utility, of claims 1-6 pertaining to lack of a specific and substantial utility, or a well established utility, remains for reasons already of record in paper No.10.

Applicant recites legal standard on pages 6-7.

Applicant argues that none of the cited references specifically address the use of breast cancer cell lines in the study of breast cancer detection and diagnosis, in particular the BT20 cell line. Applicant asserts that these references mostly address the fact that cell culture models, alone, do not reliably predict the effects of potential therapeutic agents on *in vivo* tumors. None of these articles specifically address the issue as to whether or not cell lines, such as BT20, are suitable for identifying genes specifically expressed, or differentially expressed, in various human cancers.

Applicant asserts that Wistuba et al attests to the generally acceptable use of breast cancer cell lines derived from primary breast carcinomas as suitable model systems for biomedical studies, Applicant asserts that while Wistuba et al do not specifically recite the BT20 cell lines, it clearly makes the point that the principle problem with using cell lines for screening studies is the ability to successfully culture them for long periods of time, and therefore, those that can be serially cultured are reliable models for breast cancer. Applicant recite the references by Zhou et al which use the breast cell line HBL-100, Sager et al, which use mammary and prostate tumor cells in culture, Lee et al, which use mammary carcinoma cell in culture, including the BT20 cell line, and Williams et al, which use the colon tumor cell lines, all in studying the expression of various genes. Applicant further submits additional references by Mitchell et al, Williamson et al, and Chen et al, which use the BT20 mammary carcinoma cell line as models for studying the expression of genes associated with human breast cancer.

The recitation of legal standard, and the references by Wistuba et al, Zhou et al, Sager et al, Lee et al, Williams et al, Mitchell et al, Williamson et al, and Chen et al is acknowledged.

Applicant's arguments set forth in paper No.11 have been considered but are not deemed to be persuasive for the following reasons:

The Examiner agrees that there is a wide spread use of tumor cell lines in studying expression of various genes, as shown the references cited by Applicant. However, as taught by Wistuba et al, despite the pivotal role played by human tumor

cell lines in biomedical research, there is a widespread belief in the scientific community that they are not representative of the tumors from which they were derived, due to extensive chromosomal rearrangements, oncogene mutations, and multiple sites of allelic loss and gene amplification in tumor cell lines, including breast carcinoma cell lines (p.2931, second column, paragraph before last). This statement is further confirmed by Drexler et al, Embleton et al, Hsu et al, Mustafa et al, Freshney et al, Dermer et al, all of record. Further, although some of the breast cancer cell lines studied by Wistuba et al have correlation with their corresponding tumor tissue, concerning various criteria such as morphological features, presence of aneuploidy, immunohistochemical expression of estrogen receptors etc.., it seems that the cell lines studied by Wistuba et al are only from a specific subset of primary breast carcinoma. The breast cell line BT20 used in the claimed invention, however, seems not to be from the same subset of primary breast carcinoma taught by Wistuba et al. Further, the period of culture of the cell lines studied by Wistuba et al during which the retention of the parental tumors are retained is only up to 60 months. It is not clear how long the cell line BT20 has been in culture, especially it is well known in the art that cell lines could have been in culture for years and years. Thus, in view of the above, it is unpredictable that the cell line BT20 has any of the properties of the cell lines studied by Wistuba et al, and retain many of the properties of their parental tumors, and one cannot determine whether that the putative overexpression of the claimed sequence in the breast cell line BT20 is not due to cell culture artifacts.

Further, it seems that the data from Table 1 is the results of electronic Northern, as disclosed on page 35. The electronic Northern findings however do not confer utility on SEQ ID NO:2. It is known in the art that the cDNA libraries used for the electronic Northerns are made up of a "representative" population of clones which are isolated and sequenced from a library source. It is noted that the representative population of the Incyte transcript libraries is not disclosed in table 1 nor in the specification. However, the Examiner takes note that cells in the human body encode approximately 100,000 genes of which between 10,000 and 20,000 are thought to be expressed as mRNAs. It is not clear that all of the genes expressed as mRNAs are represented in the libraries in the claimed invention. The identification of SEQ ID NO:2 in the selected, incomplete libraries appears to be a serendipitous event.. The fact that the claimed polynucleotide is not expressed in one library or is expressed in another appears to be an artifact of the analytical system and cannot be extrapolated to a prediction of whether that molecule is expressed in the tissue "represented" by the library. It is not possible to determine from the information in the specification whether SEQ ID NO:2 could be useful in cancer research or as a marker for cancer cells without further research on the material itself.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 1-6 remain rejected under 112, first paragraph, enablment due to lack of a specific, substantial utility or a well established utility for reasons already of record.

The same arguments and reasons for rejection as set forth under 101 rejection apply here as well.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claims 1(b), 2(b), 3-6 remain rejected under 112, first paragraph for lacking a clear written description of a polynucleotide encoding a naturally occurring amino acid sequence having at least 95% sequence identity to SEQ ID NO:1, or a naturally occurring polynucleotide having at least 95% sequence identity to SEQ ID NO:21, for reasons already of record in paper No: 10.

Applicant asserts that given SEQ ID NO:1 and 2, and the described chemical and structural features of SEQ ID NO:1, one of kill in the art would recognize naturally occuring variants of SEQ ID NO:1, having at least 95% sequence identity to SEQ ID NO:1

Applicant further asserts as follows: 1) In constrast to the situation of *Lilly* and *Fiers*, the present application defines polynucleotides in terms of chemical structure, rather than on functional characteristics. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NOs:1 and 2 2) The claimed genus is of narrow scope. Brenner al teach that 30% identity is a reliable threshold for establishing evolutionary homology between the two aligned sequences over at least 150 residues. In accordance with Brenner al, naturally occurring molecules may exist which could be characterized as mucin-related protein, and which have as little as 40% identity over at least 70 residues to DEQ ID NO:1..The present claims recite a polynucleotide encoding a polypeptide comprising a naturally occurring amino acid sequence having at least 95% sequence identity to SEQ ID NO:1, which has 946 amino

acid residues. This variation is far less than 30% identity over at least 150 residues to SEQ ID NO:1, and 3) The state of the art at the time the invention was made is further advanced than at the time of the *Lilly* and *Fiers* application, for example, PCR, highly effecient cloning and DNA sequencing technology, large databases of protein and nucleic acid sequences, all of which did not exist at the time of the *Lilly* and *Fiers* application.

Applicant's arguments in paper No:11 have been considered but are not deemed to be persuasive for the following reasons:

Contrary to Applicant's assertion, the subject matter of the present claims is not defined in terms of the chemical structure of SEQ ID NOs:1 and 2, and one of kill in the art would not be able to identify naturally occurring variants of SEQ ID NO:1, having at least 95% sequence identity to SEQ ID NO:1.

The claims as written clearly read on allelic variant polynucleotides of the polynucleotide of SEQ ID NO:2, or allelic polynucleotides encoding variant polypeptides of the polypeptide of SEQ ID NO:1. No disclosure of the claimed allelic variant polynucleotides beyond the mere mention of variants and allelic sequences is made in the specification. The claims encompass allelic variant polynucleotides encoding polypeptide variants having any type of substitution by nature besides conservative substitution, or deletion by nature at any amino acid, throughout the length of the peptide, provided the changes are within 5% of the sequence identity. The specification does not disclose which amino acid subjected to conservative or non-conservative substitution, or deletion by nature, the type of substitution besides conservative

substitution by nature, nor the type of amino acids replacing the original amino acids. Thus the scope of the claims includes numerous structural polynucleotide variants. No common structural attributes that identify the claimed polynucleotide variants are disclosed. In addition, no common functional attributes that identify the claimed polynucleotide variants are disclosed, because the function of a polypeptide encoded by a polynucleotide could be abolished, even with substitution of only one amino acid of the polypeptide (Burgess et al), and because the function of SEQ ID NO:1 is not known (see the above Utility rejection). The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed naturally occurring polynucleotide variants, SEQ ID NOs:1 and 2 alone are insufficient to describe said variants. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of polynucleotide variants and that Applicant was not in possession of the naturally occurring variant polynucleotides, and polynucleotides encoding naturally occurring polypeptide variants.

Further, in the absence of a teaching of the chemical structure of the claimed numerous polynucleotide variants, and polynucleotides encoding naturally occurring polypeptide variants, even with the advance of technology at the time the invention was made, one of skill in the art still could not identify the numerous claimed naturally occurring polynucleotide variants, and polynucleotides encoding naturally occurring polypeptide variants, using any of the cited technology, such as PCR, highly efficient

cloning and DNA sequencing technology, large databases of protein and nucleic acid sequences. Thus the recited case law *Lilly* and *Fiers* still applies well to the present application, despite the advance of technology at the time the invention was made.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. Rejection under 35 USC 112, first paragraph of claims 1, 3-6 pertaining to lack of enablement for a polynucleotide "encoding" the polypeptide of SEQ ID NO:1, and a method of making said polypeptide remains for reasons already of record in paper No: 10.

Applicant asserts as follows: While steady state mRNA levels are not always directly proportional to the amount of protein in a cell, mRNA levels are routinely used as an indicator of protein expression. Countless publications have been based on data relating to mRNA levels when the polypeptide encoded by the mRNA was unknown or difficult to detect. Applicant asserts that the examples recited by the Office represent unusual mechanisms of gene regulation. Applicant recites a reference by Lewin B., stating that for most genes control at the stage of initiation, i.e. by the interaction of RNA polymerase with its promoter is a major control point and probably the most common level of regulation. Moreover, Applicant asserts that one of skill in the art would conclude that mRNA levels are routinely used as an indicator of protein expression and that mRNA levels are usually a good indicator of protein levels in a cell.

Applicant further asserts that one would be imprudent in assuming that protein levels did not correspond to mRNA levels and that levels of SEQ ID NO:1 were controlled predominantly in a post-transcriptional manner.

The recitation of the reference by Lewin B. is acknowledged.

Applicant's arguments in paper No: 11 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that the Lewin reference does not support Applicant's statement that mRNA levels are routinely used as an indicator of protein expression and that mRNA levels are usually a good indicator of protein levels in a cell, because the Lewin reference does not disclose a correlation between mRNA and protein levels of expression. It only discloses that most genes control at the stage of initiation i.e. by the interaction of RNA polymerase with its promoter, initiation is a major control point and probably the most common level of regulation.

It is further noted that the Examiner did not recite that the levels of SEQ ID NO:1 are controlled predominantly in a post-transcriptional manner.

Further, the claimed polynucleotide of SEQ ID NO:2 and the putative encoded polypeptide of SEQ ID NO:1 lacks a specific, substantial or well established utility, *supra* (see rejection under 101, utility above).

It is unpredictable that SEQ ID NO:1, which is a deduced amino sequence from the polynucleotide of SEQ ID NO:2, is expressed in disease tissues in nature and /or overexpressed in disease tissues as compared to normal tissues. The references by Alberts et al, Shantz et al, and Fu et al clearly indicate that the presence of mRNA does

not always dictate that such mRNAs are translated into proteins, and that the predictability of protein translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. For example, the p53 protein levels of expression do not correlate with levels of p53 mRNAs, and the p53 protein could be undetectable in cells expressing abundant amount of wild type p53 mRNA (Fu et al, figure 3, and page 4396, second column). Further, the intracellular half-life of ornithine decarboxylase is less than 1 hour, and the post-translational regulation of the degradation of said enzyme is depending on the level of polyamines (Shantz et al, page 110, first column).

Moreover, concerning Applicant's assertion that the examples recited by the Office represent unusual mechanisms of gene regulation, the arguments are not persuasive, because although some of the genes studied in the cited publication include special structural elements responsible for the observed translational regulation, the recited references by the Examiner are only some of examples of negative translational regulation. It is well known in the art that both translational and post-translational control is an important step in the control of gene expression, and although in some cases translational control could be specific and requires some structural pecularities, it is not necessarily that the translational control require structural pecularities (Jansen M, 1995, Pediatric Res, 37(6): 681-686).

2. Claims 1(b), 2(b), 3-6 remain rejected under 112, first paragraph for lacking enablement for a polynucleotide encoding a naturally-occurring amino acid sequence having at least 95% sequence identity to SEQ ID NO:1, or a naturally occurring

polynucleotide having at least 95% sequence identity to SEQ ID NO:2, for reasons already of record in paper No:10.

Applicant argues that the variants are described in chemical and structure terms, rather than function, and there is therefore no requirement for the claimed variants to be capable of function as that which is disclosed. Applicant argues that one would be able to identify the claimed variants from naturally occurring mucin-related proteins or polynucleotides based on the disclosure discussed previously, and to make said variants by chemical methods routine in the art.

Applicant argues that the claimed variants could be used for hybridization probes, for the diagnosis of disease conditions, for chromosome mapping, and in microarray assays to monitor gene expression patterns. Applicant argues that none of the described uses of the polynucleotides require a functional association of an encoded polypeptide. Applicant argues that in particular the use of various polypeptides of the invention in hybridization, amplification, and screening technology to identify and distinguish among SEQ ID NO:2 and related molecules in a sample does not depend on whether or not such variants might be non-functional.

Applicant's arguments in paper No:11 have been considered but are not deemed to be persuasive for the following reasons:

Applicant has not taught how to use the invention for the reasons previously set forth for utility. Thus since there is no practical, specific, and substantial uses for the sequence of SEQ ID NO:2, or the predicted encoded SEQ ID NO:1 and variants thereof in diagnosis of disease conditions, or in microarray for reasons set forth in utility

rejection, other cited uses of the claimed variants of SEQ ID NO:2 such as hybridization probes, chromosome mapping, amplification, and screening technology to identify and distinguish among SEQ ID NO:2 and related molecules in a sample would not have any practical use either.

Further, no consensus sequences that identify the claimed polynucleotide variants are disclosed, *supra*, and thus one cannot identify the claimed variants.

Moreover, identification of the claimed variants, based solely on sequence homology would result in compounds with unknown function, since the unpredictability of utilizing predicted structural determinations to ascertain functional aspects of the protein is demonstrated by Bork and Scott et al, *supra* (see rejection under 101, utilty above), and thus one cannot predict that the claimed naturally occurring variants that are screened by PCR, based solely to 95% identity with SEQ ID NO:or 2 would function as claimed . Bork teaches the pitfalls associated with comparative sequence analysis for predicting protein function and specifically states that conclusions from comparison analysis are often stretched with regard to protein products and specifically cites that most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality. The teaching of Scott et al further confirms the teaching of Bork, wherein Scott et al teach an example of misidentification of the function of a protein based on homology alone, and conclude that it is important to confirm the function of a newly identified gene products even when the database reveal significant homology to proteins of known function.

Thus, one of skill in the art would not know how to use the claimed variants based solely on screening sequences having sequence homology to SEQ ID NO:2, nor how make a polynucleotide encoding a polypeptide comprising a naturally occurring amino acid sequence having at least 95% sequence identity with SEQ ID NO:1, so that they would function as claimed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

May 15, 2003

SUSAN UNGAR, PH.D
PRIMARY EXAMINER